First Hit

L1: Entry 1 of 2 File: JPAB Oct 31, 2000

PUB-NO: JP02000302633A
DOCUMENT-IDENTIFIER: JP 2000302633 A
TITLE: ENDOTHELIN-CONVERTING ENZYME INHIBITOR

PUBN-DATE: October 31, 2000

INVENTOR-INFORMATION:
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ASSIGNEE-INFORMATION:
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APPL-NO: JP11109766
APPL-DATE: April 16, 1999

INT-CL (IPC): A61 K 7/00; A61 K 7/48; A61 P 17/00; A61 P 43/00; A61 K 35/78; C12 N 9/99

ABSTRACT:

PROBLEM TO BE SOLVED: To obtain the subject inhibitor with plant extract(s) as active ingredient.

SOLUTION: This inhibitor contains, as active ingredient, extract(s) from at least one kind of plant selected from the group consisting of Crataegus oxyacantha L., Sanguisorba officinalis L., Syzygium aromaticum Merrill et Perry, Rosamultiflora Thunberg, Uncaria gambir Roxburch, Tilia platyphyllos Scop., Glycyrrhiza uralensis Fisher, Morus alba Linne, Rosmarinus officinalis L., Thea sinensis Linne var., Betula platyphylla Sukatschev var., Potentilla tormentilla Vulgaris L., Thymus vulgaris L., Gentiana lutea L., Geranium thunbergii, Panax ginseng C.A. Mayer, Cinchona succirubra Pavon, Swertia japonica (Schult.) Makino, Centellaasiatica, L., Artemisia capillaris Thunb, Rehmannia glutinosa Libosch., Lonicera japonica Thunb, and Mentha piperita L.

First Hit

End of Result Set

L1: Entry 2 of 2 File: DWPI Sep 2, 2003

DERWENT-ACC-NO: 2001-127629
DERWENT-WEEK: 200358

TITLE: Endothelin converting enzyme inhibitor for treating pulmonary hypertension, ischemic heart disease, chronic renal insufficiency, comprises specific plant extracts as the active ingredient

PATENT-ASSIGNEE:

ASSIGNEE	CODE
KAO CORP	KAOS

PRIORITY-DATA: 1999JP-0109766 (April 16, 1999)

Search Selected | Search ALL | Clear

PATENT-FAMILY:

	PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
☐	JP 3441395 B2	September 2, 2003		006	A61K007/00
☐	JP 2000302633 A	October 31, 2000		006	A61K007/00

APPLICATION-DATA:

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JP 3441395B2	April 16, 1999	1999JP-0109766	
JP 3441395B2		JP2000302633	Previous Publ.
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INT-CL (IPC): A61 K 7/00; A61 K 7/48; A61 K 35/78; A61 P 17/00; A61 P 43/00; C12 N 9/99

ABSTRACTED-PUB-NO: JP2000302633A
BASIC-ABSTRACT:

NOVELTY - Endothelin converting enzyme (ECE) inhibitor comprises specific plant extract as active ingredient.

DETAILED DESCRIPTION - ECE inhibitor comprises plant extract of Crataegus oxyacantha, Sanguisorba officinalis, clove, Rosamultiflora fructus, gambir, linden, licorice, mulberry bark, rosemary, Assam tea, white birch, tormentilla, thyme, Gentiana, Geranium thumbergii, ginseng, cinchona succirubra, swertia, Centella asiatica, Artemisia capillaris, rehmannia root, Lonicera japonica and/or Mentha piperita, as active ingredient(s).

ACTIVITY - Antiallergic, antiinflammatory,

MECHANISM OF ACTION - ECE inhibition; testosterone 5 alpha -reductase inhibition; superoxide elimination; hyaluronidase deactivation; androgen receptor binding inhibition; interleukin-4 production inhibition. ECE extract prepared from human culture vascular endothelial cell was added to 0.1 M sodium phosphate buffer (pH 6.8). Initial concentration of extract was 2 mu g and final concentration was 1 v/v %. 0.1 mu M human serine was added. Assay of endothelin production was performed and result show a fixed quantity of endothelin production. Standard solution containing 100 mu L of reaction solution and the human endothelin was diluted. 0.3 mu g of anti-endothelin 1 rabbit Fab' peroxidase label antibody was added to plate. 100 mu l of 1N sulfuric acid was added and the reaction was stopped. Subsequently ELISA plate was used and absorbance was measured at 490 nm. ECE inhibitory activity was evaluated. A control (without plant extract) was proceeded as above. The plant extract showed excellent ECE inhibitory activity of 96.5% or more of clove.

USE - ECE is a vaso constrictor for treating pulmonary hypertension, or treats ischemic heart disease, or chronic renal insufficiency.

ADVANTAGE - ECE inhibitor effectively inhibits the conversion of endothelin.

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: CONVERT ENZYME INHIBIT TREAT PULMONARY HYPERTENSIVE ISCHAEMIC HEART DISEASE CHRONIC RENAL INSUFFICIENCY COMPRISE SPECIFIC PLANT EXTRACT ACTIVE INGREDIENT

DERWENT-CLASS: B04 D21

CPI-CODES: B04-A08; B04-A08C2; B04-A09; B04-A09A; B04-A09D; B04-A09G; B04-A10; B04-A10B; B04-A10F; B04-A10H; B11-C07A4; B11-C08E1; B12-K04A; B14-C03; B14-D02; B14-D03; B14-D05D; B14-F02A; B14-F02C; B14-F02D; B14-G02A; B14-L07; B14-N10; D08-B09;

CHEMICAL-CODES:

Chemical Indexing M1 *01*
Fragmentation Code
M423 M431 M782 M905 N103 N104 N161 P420 P431 P520
P523 P525 P528 P611 P612 P613 P614 P616 P617 P723
Q262
Specfic Compounds
A00GTK A00GTT A00GTM

Chemical Indexing M1 *02*
Fragmentation Code
M423 M431 M782 M905 N103 N104 N161 P420 P431 P520
P523 P525 P528 P611 P612 P613 P614 P616 P617 P723
Q262
Specfic Compounds
A04BPK A04BPT A04BPM

Chemical Indexing M1 *03*
Fragmentation Code
M423 M431 M782 M905 N103 N104 N161 P420 P431 P520
P523 P525 P528 P611 P612 P613 P614 P616 P617 P723
Q262
Specfic Compounds
A1RH4K A1RH4T A1RH4M

Chemical Indexing M1 *04*
Fragmentation Code

M423 M431 M782 M905 N103 N104 N161 P420 P431 P520
P523 P525 P528 P611 P612 P613 P614 P616 P617 P723
Q262
Specfic Compounds
A04BMK A04BMT A04BMM

Chemical Indexing M1 *05*
Fragmentation Code
M423 M431 M782 M905 N103 N104 N161 P420 P431 P520
P523 P525 P528 P611 P612 P613 P614 P616 P617 P723
Q262
Specfic Compounds
A2N34K A2N34T A2N34M

Chemical Indexing M1 *06*
Fragmentation Code
M423 M431 M782 M905 N103 N104 N161 P420 P431 P520
P523 P525 P528 P611 P612 P613 P614 P616 P617 P723
Q262
Specfic Compounds
A0879K A0879T A0879M

Chemical Indexing M1 *07*
Fragmentation Code
M423 M431 M782 M905 N103 N104 N161 P420 P431 P520
P523 P525 P528 P611 P612 P613 P614 P616 P617 P723
Q262
Specfic Compounds
A0FEQK A0FEQT A0FEQM

SECONDARY-ACC-NO:
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					Ｗ	４Ｃ０８８
	7/48			7/48		
Ａ６１Ｐ	17/00			31/00	６１７	
	43/00				６４３Ｄ	

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最終頁に続く

(54)【発明の名称】　エンドセリン変換酵素阻害剤

(57)【要約】
【課題】　植物抽出物を有効成分とするエンドセリン変換酵素阻害剤の提供。
【解決手段】　セイヨウサンザシ、ワレモコウ、チョウジ、エイジツ、アセンヤク、ボダイジュ、甘草、ソウハクヒ、ローズマリー、アッサムチャ、シラカバ、トルメンチラ、タイム、ゲンチアナ、ゲンノショウコ、ニンジン、キナノキ、センブリ、ツボクサ、カワラヨモギ、ジオウ、スイカズラ及びセイヨウハッカからなる群より選ばれる１種以上の植物の抽出物を有効成分とするエンドセリン変換酵素阻害剤。

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【特許請求の範囲】

【請求項1】 セイヨウサンザシ、ワレモコウ、チョウジ、エイジツ、アセンヤク、ボダイジュ、甘草、ソウハクヒ、ローズマリー、アッサムチャ、シラカバ、トルメンチラ、タイム、ゲンチアナ、ゲンノショウコ、ニンジン、キナノキ、センブリ、ツボクサ、カワラヨモギ、ジオウ、スイカズラ及びセイヨウハッカからなる群より選ばれる1種以上の植物の抽出物を有効成分とするエンドセリン変換酵素阻害剤。

【発明の詳細な説明】

【0001】

【発明の属する技術分野】本発明は、エンドセリン変換酵素（以下「ECE」という）阻害剤に関する。

【0002】

【従来の技術】エンドセリンは、強力な血管収縮作用を有し、肺高血圧症、虚血性心疾患、慢性腎不全等の発症因子であることが示唆されている（Jpn. Pharmacol. 1992;58;279p等）。かかるエンドセリンは、ECEによって、ビッグエンドセリン（プロエンドセリン）から開裂、生成される。したがってECEを阻害すれば、上記疾患の予防、治療等に有効であると考えられる。このため、ECE阻害剤の探求が行われ、例えば特定のキナゾリン誘導体（特表平10-510834号公報）等が知られている。

【0003】

【発明が解決しようとする課題】しかし、有効かつ安全で応用範囲の広いECE阻害剤が求められていた。

【0004】

【課題を解決するための手段】本発明者は、広範囲の植物のうち、特定の植物の抽出物が、高いECE阻害効果を有することを見出した。

【0005】すなわち本発明は、セイヨウサンザシ、ワレモコウ、チョウジ、エイジツ、アセンヤク、ボダイジュ、甘草、ソウハクヒ、ローズマリー、アッサムチャ、シラカバ、トルメンチラ、タイム、ゲンチアナ、ゲンノショウコ、ニンジン、キナノキ、センブリ、ツボクサ、カワラヨモギ、ジオウ、スイカズラ及びセイヨウハッカからなる群より選ばれる1種以上の植物の抽出物を有効成分とするECE阻害剤を提供するものである。

【0006】

【発明の実施の形態】本発明に使用される植物は、セイヨウサンザシ（Crataegus oxyacantha L.）、ワレモコウ（Sanguisorba officinalis L.）、チョウジ（Syzygium aromaticum Merrill. et Perry）、エイジツ（Rosa multiflora Thunberg）、アセンヤク（Uncaria gambir Roxburch）、ボダイジュ（Tilia platyphyllos Scop.）、甘草（Glycyrrhiza uralensis Fisher）、ソウハクヒ（Morus alba Linne）、ローズマリー（Rosmarinus officinalis L.）、アッサムチャ（Thea sinensis Linne var.）、シラカバ（Betula platyphylla Sukatschev var.）、トルメンチラ（Potentilla tormentilla Vulgaris L.）、タイム（Thymus vulgaris L.）、ゲンチアナ（Gentiana lutea L.）、ゲンノショウコ（Geranium thunbergii）、ニンジン（Panax ginseng C. A. Mayer）、キナノキ（Cinchona succirubra Pavon）、センブリ（Swertia japonica (Schult.) Makino）、ツボクサ（Centellaasiatica L.）、カワラヨモギ（Artemisia capillaris Thunb.）、ジオウ（Rehmannia glutinosa Libosch.）、スイカズラ（Lonicera japonica Thunb.）及びセイヨウハッカ（Mentha piperita L.）からなる群より選ばれるものである。

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【0007】このうち、ワレモコウは止血及び血小板増加作用；チョウジ、エイジツ、アセンヤク、甘草、ジオウはテストステロン5α-リダクターゼ阻害作用；ボダイジュは抗アレルギー作用；ローズマリー、ゲンノショウコ、キナノキはスーパーオキサイド消去作用；アッサムチャはヒアルロニダーゼ失活作用；シラカバ、ゲンチアナは抗炎症作用；タイム、カワラヨモギは養毛・育毛作用；ニンジン、センブリはアンドロゲン受容体結合阻害作用；ツボクサ、スイカズラはインターロイキン4産生抑制作用等を有することが知られている。しかし、これらの植物がECE阻害作用を有することは全く知られていなかった。

【0008】本発明に用いる上記植物の抽出物には、植物の全草又はそれらの葉、葉柄、茎、根、種子の1以上を、乾燥し又は乾燥せずに、そのまま、又は粉砕後、常温又は加温下で溶媒抽出するか、ソックスレー抽出器等の抽出器具にて抽出するか、二酸化炭素等の超臨界ガスで抽出するか、又は水蒸気蒸留、圧搾等の方法により得られる抽出液、その稀釈液もしくは濃縮液、又は乾燥粉末等が含まれる。

【0009】抽出溶媒としては、水；メタノール、エタノール、プロパノール、ブタノール等のアルコール類；プロピレングリコール、ブチレングリコール等の多価アルコール；アセトン、メチルエチルケトン等のケトン類；酢酸メチル、酢酸エチル等のエステル類；テトラヒドロフラン、ジエチルエーテル等の鎖状及び環状エーテル類；ジクロロメタン等のハロゲン化炭化水素類；ヘキサン、シクロヘキサン、石油エーテル等の炭化水素類；トルエン等の芳香族炭化水素類；ポリエチレングリコール等のポリエーテル類；ピリジン類等が挙げられ、これらを単独又は2種以上混合して用いることができる。

【0010】抽出は、上記植物の全草等に溶媒を加え、好ましくは1～100℃、特に好ましくは3～70℃で、好ましくは0．5～30日間、特に好ましくは1～15日間行う。得られた抽出液を適宜静置、沪過等して植物抽出物を得ることができる。かかる抽出物は、液液分配、可溶媒沈殿物の除去等により、上記抽出物から不活性な夾雑物を除去し、さらに必要により公知の方法で脱臭、脱色してもよい。さらにゲル沪過、クロマトグラ

フィー、精密沪過等により活性の高い画分を分画してもよい。

【００１１】上記植物の抽出物は、そのままでＥＣＥ阻害剤として用いることができるが、適宜製剤化してもよい。本発明のＥＣＥ阻害剤中の、上記植物の抽出物の含有量は、効果、配合性、使用感等の観点から、固形分換算で０．００００１～２０重量％、特に０．０００１～１０重量％が好ましい。

【００１２】本発明のＥＣＥ阻害剤は、外用、内服のいずれの方法でも投与することができるが、外用投与、特に皮膚外用剤の形態とすることが好ましい。その剤型は、目的に応じて任意に選択でき、クリーム状、軟膏状、乳液状、ローション状、溶液状、ゲル状、パック状、パウダー状、スティック状等にできる。また、本発明のＥＣＥ阻害剤は、化粧料、医薬部外品、医薬品等として用い得る。

【００１３】本発明のＥＣＥ阻害剤は、本発明の効果を損なわない範囲で、化粧料、医薬部外品、医薬品等に一般に用いられる精製水、エタノール、油性物質、保湿剤、増粘剤、防腐剤、乳化剤、薬効成分、粉体、紫外線吸収剤、色素、香料、乳化安定剤、ｐＨ調整剤等を配合し、常法に従って製造できる。かかるＥＣＥ阻害剤は、肺高血圧症、虚血性心疾患等の疾病の予防、治療等に利用できる。

【００１４】ＥＣＥには、エンドセリン１、エンドセリン２、エンドセリン３等があるが、本発明のＥＣＥ阻害剤は、そのいずれにも有効である。

【００１５】

【実施例】製造例１　セイヨウサンザシエキスの調製

セイヨウサンザシ（Crataegus oxyacantha Linne）の果実１０ｇに水とエタノールとの混液（５０：５０）１００mlを加え、室温下、ときどき撹拌しながら、２４時間抽出した。これを沪過し、水とエタノールとの混液（５０：５０）を加え、全体を１００mlに調製した。

【００１６】製造例２　ワレモコウエキスの調製

ワレモコウ（Sanguisorba officinalis Linne）の根及び根茎を細切し、その１０ｇに水とエタノールとの混液（５０：５０）１００mlを加え、室温下、ときどき撹拌しながら、２４時間抽出した。これを沪過し、沪液に活性炭４ｇを加え、室温下、２４時間撹拌した。これを沪過し、水とエタノールとの混液（５０：５０）を加え、全体を１００mlに調製した。

【００１７】製造例３　チョウジエキスの調製

チョウジ（Syzygium aromaticum Merrill et Perry）のつぼみ１０ｇに水とエタノールとの混液（５０：５０）１００mlを加え、室温下、ときどき撹拌しながら、２４時間抽出後、沪過した。これに水１００mlを加え４０℃、減圧下、約２０mlまで濃縮した。この操作を５回行なった後、水及びエタノールを加えてエタノール濃度を５０ｖ／ｖ％にし、全体を１００mlに調製した。

【００１８】製造例４　エイジツエキスの調製

製造例１において、セイヨウサンザシの代りに粉砕したノイバラ（Rosa multiflora Thunberg）を用いた以外は、製造例１と同様にしてエイジツエキスを調製した。

【００１９】製造例５　アセンヤクエキスの調製

製造例１において、セイヨウサンザシの果実の代りにガンビールノキ（Uncaria ganbir Roxburgh）の葉及び若枝を水で煮て製した乾燥エキス（アセンヤク）を用いた以外は、製造例１と同様にしてアセンヤクエキスを調製した。

【００２０】製造例６　ボダイジュエキスの調製

フユボダイジュ（Tilia cordata Miller）の花を細切し、その１０ｇに水とプロピレングリコールとの混液（５８：４２）１００mlを加え、室温下、ときどき撹拌しながら、２４時間抽出した。これを沪過し、水とプロピレングリコールとの混液（５８：４２）を加え、全体を１００mlに調製した。

【００２１】製造例７　甘草エキスの調製

甘草（Glycyrrhiza glabra Linne）の根を細切し、その５ｇに水とエタノールとの混液（５：９５）１５mlを加え、浸漬した。これを沪過し、得られた抽出液を濃縮し、固形分３２５mgを得た。これに酢酸エチル１０mlを加え、再び沪過を行ない不溶分を除去し、甘草エキスを得た。この甘草エキスを濃縮したところ、その固形分は５６mgであった。

【００２２】製造例８　ソウハクヒエキスの調製

製造例１において、セイヨウサンザシの果実の代りにマグワ（Morus alba Linne）の根皮を細切したものを用いた以外は、製造例１と同様にしてソウハクヒエキスを調製した。

【００２３】製造例９　ローズマリーエキスの調製

製造例１において、セイヨウサンザシの果実の代りにマンネンロウ（Rosmarinus officinalis Linne）の葉及び花を細切したものを用いた以外は、製造例１と同様にしてローズマリーエキスを調製した。

【００２４】製造例１０　アッサムチャエキスの調製

製造例１において、セイヨウサンザシの果実の代りにアッサムチャ（Thea sinensis Linne var. assamica Pierre）の葉より製したもの（紅茶）を用いた以外は、製造例１と同様にしてアッサムチャエキスを調製した。

【００２５】製造例１１　シラカバエキスの調製

製造例１において、セイヨウサンザシの果実の代りにヨーロッパシラカバ（Betula pendula Roth.）の樹皮及び木部を細切したものを用いた以外は、製造例１と同様にしてシラカバエキスを調製した。

【００２６】製造例１２　トルメンチラエキスの調製

製造例１において、セイヨウサンザシの果実の代りにトルメンチラ（Potentilla tormentilla Schrk）の根を細切したものを用い、かつ水とエタノールとの混液の代りに水を用いた以外は、製造例１と同様にしてトルメンチ

ラエキスを調製した。

【0027】製造例13　タイムエキスの調製
製造例1において、セイヨウサンザシの果実の代りにイブキジャコウソウ（thymus serpyllum Linne）の地上部を細切したものを用いた以外は、製造例1と同様にしてタイムエキスを調製した。

【0028】製造例14　ゲンチアナエキスの調製
製造例1において、セイヨウサンザシの果実の代りにゲンチアナ（Gentiana lutea Linne）の根及び根茎を粉砕したものを用いた以外は、製造例1と同様にしてゲンチアナエキスを調製した。

【0029】製造例15　ゲンノショウコエキスの調製
製造例1において、セイヨウサンザシの果実の代りにゲンノショウコ（Geranium thunbergii Siebold et Zuccarini）の地上部を細切したものを用いた以外は、製造例1と同様にしてゲンノショウコエキスを調製した。

【0030】製造例16　ニンジンエキスの調製
製造例1において、セイヨウサンザシの果実の代りにオタネニンジン（Panaxginseng C. A. Meyer）の根を粉砕したものを用いた以外は、製造例1と同様にしてニンジンエキスを調製した。

【0031】製造例17　キナエキスの調製
製造例1において、セイヨウサンザシの果実の代りにキナノキ（Cinchona succirubra Pavon et Klotzch）の樹皮を細切したものを用いた以外は、製造例1と同様にしてキナエキスを調製した。

【0032】製造例18　センブリエキスの調製
製造例1において、セイヨウサンザシの果実の代りにセンブリ（Swertia japonica Makino）の全草を細切したものを用いた以外は、製造例1と同様にしてセンブリエキスを調製した。

【0033】製造例19　ツボクサエキスの調製
製造例1において、セイヨウサンザシの果実の代りにツボクサ（Centella asiatica Linne）の葉及び茎を細切したものを用いた以外は、製造例1と同様にしてツボクサエキスを調製した。

【0034】製造例20　カワラヨモギエキスの調製
製造例1において、セイヨウサンザシの果実の代りにカワラヨモギ（Artemisia capillaris Thunberg）の頭花を細切したものを用い、かつエタノールの代りに1，3-ブタンジオールを用いた以外は、製造例1と同様にしてカワラヨモギエキスを調製した。

【0035】製造例21　ジオウエキスの調製
製造例1において、セイヨウサンザシの果実の代りにアカヤジオウ（Rehmannia glutinosa Liboschitz var. purpurea Makino）の根を粉砕したものを用いた以外は、製造例1と同様にしてジオウエキスを調製した。

【0036】製造例22　スイカズラエキスの調製
製造例1において、セイヨウサンザシの果実の代りにスイカズラ（Lonicera japonica Thunberg）の花を細切したものを用い、かつエタノールの代りに1，3-ブタンジオールを用いた以外は、製造例1と同様にしてスイカズラエキスを調製した。

【0037】製造例23　セイヨウハッカエキスの調製
製造例1において、セイヨウサンザシの果実の代りにセイヨウハッカ（Mentha piperita Linne）の葉を細切したものを用いた以外は、製造例1と同様にしてセイヨウハッカエキスを調製した。

【0038】試験例1
（1）ECEの調製
コラーゲン（1）コートしたフラスコ上でコンフルエントに増殖したヒト培養血管内皮細胞を、リン酸緩衝生理食塩水（pH7．4）で洗浄し、75cm² 当たり1mLの50mM sodium phosphate buffer（pH7．8）を加え、セルスクレイパーを用いて細胞を掻き集めた。その細胞の懸濁液をmodel GE 50 sonicator （serial 19214C ）を用いて超音波破砕し、10000g×20分、4℃の条件で遠心した。さらに上清を80000g×60分、4℃の条件で遠心し、沈澱を0．1%のTriton X-100を含む25mM sodium phosphate buffer（pH6．8）に溶解し、ECE抽出液とした。

（2）酵素反応
0．1Msodium phosphate buffer （pH6．8）、0．5M NaCl、2μgのECE抽出液、及び終濃度が1%（v／v）となるように上記植物抽出物を混合し、37℃で15分間プレインキュベートした。次いで、0．1μMヒトビッグエンドセリン1を加えて100μLとし、37℃で2時間反応させた後、5mMEDTAを100μL加えて反応を停止させた。

（3）生成エンドセリンの定量
上記で得られた反応液中のエンドセリンを、酵素免疫測定法を用いたサンドイッチ法（エンドセリン1測定キット：IBL社）により定量した。すなわち、まずヒトエンドセリン1に対するウサギIgGを固相した96穴プレートに、上記反応終了後の反応液とヒトエンドセリン1標準液を100μL添加し、37℃で1時間反応させた。ヒトエンドセリン1標準液は、1%BSA、0．05%Tween 20を含むリン酸緩衝生理食塩水（pH7．4）で稀釈して調製した。該リン酸緩衝生理食塩水（pH7．4）でプレートを洗浄後、抗エンドセリン1ウサギFab'ペルオキシダーゼ標識抗体を0．3μg添加し、37℃で30分間反応させた。該リン酸緩衝生理食塩水（pH7．4）でプレートを洗浄後、0．03%過酸化水素含有緩衝液に0．4mg／mLになるように溶解したO-フェニレンジアミン（基質）を、100μL添加した。室温暗所で15分間反応させた後、1N硫酸を100μL添加して反応を停止させた。次いでELISA プレートリーダー（model 3550：Bio-Rad 社）を用いて、490nmにおける吸光度を測定した。

（4）ECE阻害活性の算出

上記植物抽出物を含有しない場合をコントロールとして、各植物抽出物のＥＣＥ阻害活性を次の式により算出した。ＥＣＥ阻害活性＝｛１－（各植物抽出物を含有した場合の吸光度／コントロールの吸光度）｝×１００（％）。結果を表１に示す。

【００３９】

【表１】

植物抽出物	ＥＣＥ阻害活性 (% of control)
セイヨウサンザシ	96.5
ワレモコウ	95.2
チョウジ	91.5
エイジツ	88.9
アセンヤク	81.1
ボダイジュ	47.4
甘草	44.9
ソウハクヒ	40.7
ローズマリー	40.3
アッサムチャ	39.5
シラカバ	39.3
トルメンチラ	37.7
タイム	37.6
ゲンチアナ	37.3
ゲンノショウコ	34.6
ニンジン	33.4
キナノキ	32.8
センブリ	30.7
ツボクサ	28.2
カワラヨモギ	28.1
ジオウ	27.1
スイカズラ	27.0
セイヨウハッカ	25.7

＊各植物抽出物の終濃度が１％となる条件で評価

【００４０】表１より明らかなように、各植物抽出物は、優れたＥＣＥ阻害活性を示した。このうち、セイヨウサンザシ、ワレモコウ及びチョウジは、ＥＣＥ阻害活性が９０％以上であり、特に優れていた。

【００４１】

【発明の効果】本発明のＥＣＥ阻害剤を用いれば、ビッグエンドセリンからエンドセリンへの変換を有効に抑制することができる。

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(54) ENDOTHELIN-CONVERTING ENZYME INHIBITOR

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain the subject inhibitor with plant extract(s) as active ingredient.

SOLUTION: This inhibitor contains, as active ingredient, extract(s) from at least one kind of plant selected from the group consisting of Crataegus oxyacantha L., Sanguisorba officinalis L., Syzygium aromaticum Merrill et Perry, Rosamultiflora Thunberg, Uncaria gambir Roxburch, Tilia platyphyllos Scop., Glycyrrhiza uralensis Fisher, Morus alba Linne, Rosmarinus officinalis L., Thea sinensis Linne var., Betula platyphylla Sukatschev var., Potentilla tormentilla Vulgaris L., Thymus vulgaris L., Gentiana lutea L., Geranium thunbergii, Panax ginseng C.A. Mayer, Cinchona succirubra Pavon, Swertia japonica (Schult.) Makino, Centellaasiatica, L., Artemisia capillaris Thunb, Rehmannia glutinosa Libosch., Lonicera japonica Thunb, and Mentha piperita L.

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* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] Endothelin conversion enzyme inhibitor which makes an active principle the extract of one or more sorts of vegetation chosen from the group which consists of a haw, Sanguisorba officinalis, caryophylli flos, Rose Fruit, cube gambir, Tilia miqueliana, glycyrrhiza, Mulberry bark, a rosemary, ASSAMUCHA, the Betula alba, torr MENCHIRA, a time, a gentian, a Geranium thunbergii Sieb. etZucc., a ginseng, KINANOKI, a sialid, Centella asiatica, Artemisia capillaris, Rehmannia Root, Japanese honeysuckle, and a peppermint.

[Translation done.]

* NOTICES *

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to an endothelin alteration enzyme (henceforth "ECE") inhibitor.
[0002]
[Description of the Prior Art] Endothelin has a powerful vasoconstrictor action and it is suggested that they are onset factors, such as pulmonary hypertension, ischemic heart disease, and chronic renal failure, (Jpn.Pharmacol.1992;58;279p etc.). This endothelin is cleft and generated by ECE from a big-end serine (pro endothelin). Therefore, if ECE is checked, it will be thought that it is effective in prevention of the above-mentioned disease, a therapy, etc. For this reason, the pursuit of an ECE inhibitor is performed, for example, the specific quinazoline derivative (****** No. 510834 [ten to] official report) etc. is known.
[0003]
[Problem(s) to be Solved by the Invention] However, it was effective and safe and the large ECE inhibitor of the application range was called for.
[0004]
[Means for Solving the Problem] this invention person found out that the extract of specific vegetation had the high ECE inhibition effectiveness among wide range vegetation.
[0005] That is, this invention offers the ECE inhibitor which makes an active principle the extract of one or more sorts of vegetation chosen from the group which consists of a haw, Sanguisorba officinalis, caryophylli flos, Rose Fruit, cube gambir, Tilia miqueliana, glycyrrhiza, Mulberry bark, a rosemary, ASSAMUCHA, the Betula alba, torr MENCHIRA, a time, a gentian, a Geranium thunbergii Sieb. etZucc., a ginseng, KINANOKI, a sialid, Centella asiatica, Artemisia capillaris, Rehmannia Root, Japanese honeysuckle, and a peppermint.
[0006]
[Embodiment of the Invention] The vegetation used for this invention A haw (Crataegus oxyacantha L.), Sanguisorba officinalis (Sanguisorba officinalis L.), Caryophylli flos (Syzygium aromaticum Merrill.et Perry), Rose Fruit (Rosa multiflora Thunberg), Cube gambir (Uncaria gambir Roxburch), Tilia miqueliana (Tilia platyphyllos Scop.), Glycyrrhiza (Glycyrrhiza uralensis Fisher), Mulberry bark (Morus alba Linne), a rosemary (Rosmarinus officinalis L.), ASSAMUCHA (Thea sinensis Linne var.), The Betula alba (Betula platyphylla Sukatschev var.), Torr MENCHIRA (Potentilla tormentilla Vulgaris L.), A time (Thymus vulgaris L.), a gentian (Gentiana lutea L.), A Geranium thunbergii Sieb. etZucc. (Geranium thunbergii), a ginseng (Panax ginseng C.A.Mayer), KINANOKI (Cinchona succirubra Pavon), A sialid (Swertia japonica (Schult.) Makino), Centella asiatica (Centellaasiatica L.), Artemisia capillaris (Artemisia capillaris Thunb.), It is chosen out of the group which consists of Rehmannia Root (Rehmannia glutinosa Libosch.), Japanese honeysuckle (Lonicera japonica Thunb.), and a peppermint (Mentha piperita L.).
[0007] Among these, as for testosterone 5alpha-reductase inhibitory action; Tilia miqueliana, it is known

[Sanguisorba officinalis] for hemostasis and thrombocytosis operation; caryophylli flos, Rose Fruit, cube gambir, glycyrrhiza, and Rehmannia Root, as for an antiallergic operation; rosemary, a Geranium thunbergii Sieb. etZucc., and KINANOKI that in the hyaluronidase deactivation operation; Betula alba and a gentian hair growing and a hair-fostering operation; ginseng, and a sialid have androgen receptor joint inhibitory action; Centella asiatica, and, as for Japanese honeysuckle, an anti-inflammatory activity; time and Artemisia capillaris have [super oxide elimination operation; ASSAMUCHA] interleukin 4 production depressant action etc. However, it was not known at all that these vegetation has ECE inhibitory action.

[0008] Without drying one or more [of the vegetable entire plants or those leaves, a petiole, a stem, a root, and a seed] in the extract of the above-mentioned vegetation used for this invention, or drying to it as it is or after grinding, ordinary temperature, or warming -- the extract which carries out solvent extraction in the bottom, extracts with extractor implements, such as a Soxhlet extractor, extracts by supercritical gas, such as a carbon dioxide, or is obtained by approaches, such as steam distillation and squeezing, its dilution liquid, concentration liquid, or desiccation powder is contained.

[0009] As an extracting solvent, alcohols; propylene glycols, such as a water; methanol, ethanol, propanol, and a butanol, Polyhydric alcohol, such as a butylene glycol; Ketones; methyl acetate, such as an acetone and a methyl ethyl ketone, Ester, such as ethyl acetate; Halogenated hydrocarbon; hexanes, such as the shape of a chain, such as a tetrahydrofuran and diethylether, and cyclic ether; dichloromethane, polyethers; pyridines [, such as hydrocarbons; toluene, /, such as an aromatic hydrocarbon; polyethylene glycol,], such as a cyclohexane and the petroleum ether, etc. are mentioned, and independent in these -- or two or more sorts can be mixed and it can use.

[0010] An extract adds a solvent to the entire plant of the above-mentioned vegetation etc., preferably, 1-100 degrees C, is 3-70 degrees C preferably, and is especially performed for one - 15 days for 0.5 - 30 days. Standing, filtration, etc. can carry out the obtained extract suitably, and a plant extract can be obtained. By removal of liquid-liquid distribution and meltable intermediation precipitate etc., this extract removes inactive impurity from the above-mentioned extract, and further, you may deodorize by the well-known approach as occasion demands, and it may decolorize. Furthermore, fractionation of the fraction with high activity may be carried out by gel filtration, the chromatography, precision filtration, etc.

[0011] The extract of the above-mentioned vegetation may be suitably pharmaceutical-preparation-ized, although it remains as it is and can use as an ECE inhibitor. Especially the content of the extract of the above-mentioned vegetation in the ECE inhibitor of this invention has 0.0001 - 10 desirable % of the weight 0.00001 to 20% of the weight at viewpoints, such as effectiveness, combination nature, and a feeling of use, to solid content conversion.

[0012] Although the ECE inhibitor of this invention can be prescribed for the patient by any approach of external use and oral administration, it is desirable to consider as the gestalt of external use administration, especially skin external preparations. The pharmaceutical form can be chosen as arbitration according to the purpose, and is made the shape of the shape of the shape of the shape of the shape of the shape of a cream, and ointment, a milk liquid, and a lotion, and a solution, gel, and a pack, and powder, in the shape of a stick, etc. Moreover, the ECE inhibitor of this invention can be used as the charge of makeup, quasi drugs, drugs, etc.

[0013] In the range which does not spoil the effectiveness of this invention, the ECE inhibitor of this invention blends the purified water generally used for the charge of makeup, quasi drugs, drugs, etc., ethanol, oily matter, a moisturizer, a thickener, antiseptics, an emulsifier, a drug effect component, fine particles, an ultraviolet ray absorbent, coloring matter, perfume, emulsion stabilizer, pH regulator, etc., and can manufacture them according to a conventional method. This ECE inhibitor is applicable to prevention of illnesses, such as pulmonary hypertension and ischemic heart disease, a therapy, etc.

[0014] Although there are endothelin 1, endothelin 2, and endothelin 3 grade in ECE, the ECE inhibitor of this invention is effective in the all.

[0015]

[Example] Example 1 of manufacture 100ml (50:50) of mixtures of water and ethanol was added to 10g

of fruits of the preparation haw (Crataegus oxyacantha Linne) of haw extractives, and it extracted under the room temperature for 24 hours, sometimes stirring. This was filtered, the mixture (50:50) of water and ethanol was added, and the whole was prepared to 100ml.
[0016] Example 2 of manufacture The fragment of the root and rhizome of preparation Sanguisorba officinalis (Sanguisorba officinalis Linne) of the Sanguisorba officinalis extractives was carried out, and 100ml (50:50) of mixtures of water and ethanol was added to the 10g, and it extracted under the room temperature for 24 hours, sometimes stirring. This was filtered, 4g of activated carbon was added to filtrate, and it stirred under the room temperature for 24 hours. This was filtered, the mixture (50:50) of water and ethanol was added, and the whole was prepared to 100ml.
[0017] Example 3 of manufacture 100ml (50:50) of mixtures of water and ethanol was added to 10g of buds of the preparation caryophylli flos (Syzygium aromaticum Merrill et Perry) of caryophylli flos extractives, and it filtered after the 24-hour extract under the room temperature, sometimes stirring. 100ml of water was added to this, and it condensed to about 20ml under 40 degrees C and reduced pressure. After performing this actuation 5 times, water and ethanol were added, ethanol concentration was made 50 v/v%, and the whole was prepared to 100ml.
[0018] Example 4 of manufacture In the example 1 of preparation manufacture of the Rose Fruit extractives, the Rose Fruit extractives were prepared like the example 1 of manufacture except having used Rosa polyantha (Rosa multiflora Thunberg) ground instead of the haw.
[0019] Example 5 of manufacture In the example 1 of preparation manufacture of cube gambir extractives, cube gambir extractives were prepared like the example 1 of manufacture except having used the solid extract (cube gambir) which boiled the leaf and young branch of Uncaria gambir Roxburgh (Uncaria ganbir Roxburgh) with water, and **(ed) them instead of the fruits of a haw.
[0020] Example 6 of manufacture The fragment of the flower of preparation Tilia cordata (Tilia cordata Miller) of the Tilia miqueliana extractives was carried out, and 100ml (58:42) of mixtures of water and propylene glycol was added to the 10g, and it extracted under the room temperature for 24 hours, sometimes stirring. This was filtered, the mixture (58:42) of water and propylene glycol was added, and the whole was prepared to 100ml.
[0021] Example 7 of manufacture The fragment of the root of the preparation glycyrrhiza (Glycyrrhiza glabra Linne) of a glycyrrhiza extract was carried out, and 15ml (5:95) of mixtures of water and ethanol was added to the 5g, and it was immersed in it. This was filtered, the obtained extract was condensed and 325mg of solid content was obtained. 10ml of ethyl acetate was added to this, it filtered again, insoluble matter was removed, and the glycyrrhiza extract was obtained. When this glycyrrhiza extract was condensed, that solid content was 56mg.
[0022] Example 8 of manufacture In the example 1 of preparation manufacture of the Mulberry bark extractives, the Mulberry bark extractives were prepared like the example 1 of manufacture except having used what carried out the fragment of the cortex of MAGUWA (Morus alba Linne) instead of the fruits of a haw.
[0023] Example 9 of manufacture In the example 1 of preparation manufacture of rosemary extractives, rosemary extractives were prepared like the example 1 of manufacture except having used what carried out the fragment of the leaf and flower of a rosemary (Rosmarinus officinalis Linne) instead of the fruits of a haw.
[0024] Example 10 of manufacture In the example 1 of preparation manufacture of ASSAMU tea extractives, ASSAMU tea extractives were prepared like the example 1 of manufacture except having used that (tea) in which ASSAMUCHA (Thea sinensis Linne var.assamica Pierre) carried out the product made from a leaf twist instead of the fruits of a haw.
[0025] Example 11 of manufacture In the example 1 of preparation manufacture of Betula-alba extractives, Betula-alba extractives were prepared like the example 1 of manufacture except having used what carried out the fragment of the bark and xylem of the Europe Betula alba (Betula pendula Roth.) instead of the fruits of a haw.
[0026] Example 12 of manufacture In the example 1 of preparation manufacture of torr MENCHIRA extractives, torr MENCHIRA extractives were prepared like the example 1 of manufacture except

having used water instead of the mixture of water and ethanol, using what carried out the fragment of the root of torr MENCHIRA (Potentilla tormentilla Schrk) instead of the fruits of a haw.
[0027] Example 13 of manufacture In the example 1 of preparation manufacture of time extractives, time extractives were prepared like the example 1 of manufacture except having used what carried out the fragment of the terrestrial part of Thymus serphyllum (thymus serpyllum Linne) instead of the fruits of a haw.
[0028] Example 14 of manufacture In the example 1 of preparation manufacture of gentian extractives, gentian extractives were prepared like the example 1 of manufacture except having used what ground the root and rhizome of a gentian (Gentiana lutea Linne) instead of the fruits of a haw.
[0029] Example 15 of manufacture In the example 1 of preparation manufacture of Geranium thunbergii Sieb. etZucc. extractives, Geranium thunbergii Sieb. etZucc. extractives were prepared like the example 1 of manufacture except having used what carried out the fragment of the terrestrial part of a Geranium thunbergii Sieb. etZucc. (Geranium thunbergii Siebold et Zuccarini) instead of the fruits of a haw.
[0030] Example 16 of manufacture In the example 1 of preparation manufacture of ginseng extractives, ginseng extractives were prepared like the example 1 of manufacture except having used what ground the root of Panax schinseng (Panaxginseng C.A.Meyer) instead of the fruits of a haw.
[0031] Example 17 of manufacture In the example 1 of preparation manufacture of chinae-cortex extractives, chinae-cortex extractives were prepared like the example 1 of manufacture except having used what carried out the fragment of the bark of KINANOKI (Cinchona succirubra Pavon et Klotzch) instead of the fruits of a haw.
[0032] Example 18 of manufacture In the example 1 of preparation manufacture of sialid extractives, sialid extractives were prepared like the example 1 of manufacture except having used what carried out the fragment of the entire plant of a sialid (Swertia japonica Makino) instead of the fruits of a haw.
[0033] Example 19 of manufacture In the example 1 of preparation manufacture of the Centella asiatica extractives, the Centella asiatica extractives were prepared like the example 1 of manufacture except having used what carried out the fragment of the leaf and stem of Centella asiatica (Centella asiatica Linne) instead of the fruits of a haw.
[0034] Example 20 of manufacture In the example 1 of preparation manufacture of the Artemisia capillaris extractives, the Artemisia capillaris extractives were prepared like the example 1 of manufacture except having used 1,3-butanediol instead of ethanol, using what carried out the fragment of the caput of Artemisia capillaris (Artemisia capillaris Thunberg) instead of the fruits of a haw.
[0035] Example 21 of manufacture In the example 1 of preparation manufacture of the Rehmannia Root extractives, the Rehmannia Root extractives were prepared like the example 1 of manufacture except having used what ground the root of Rehmannia glutinosa Liboschitz (Rehmannia glutinosa Liboschitz var.purpurea Makino) instead of the fruits of a haw.
[0036] Example 22 of manufacture In the example 1 of preparation manufacture of Japanese honeysuckle extractives, Japanese honeysuckle extractives were prepared like the example 1 of manufacture except having used 1,3-butanediol instead of ethanol, using what carried out the fragment of the flower of Japanese honeysuckle (Lonicera japonica Thunberg) instead of the fruits of a haw.
[0037] Example 23 of manufacture In the example 1 of preparation manufacture of peppermint extractives, peppermint extractives were prepared like the example 1 of manufacture except having used what carried out the fragment of the leaf of a peppermint (Methapiperita Linne) instead of the fruits of a haw.
[0038] The Homo sapiens culture vascular endothelial cell increased confluent on the flask which carried out the example 1 of trial (1) collagen [preparation] (1) coat of ECE is washed by phosphate buffered saline (pH7.4), and it is 2 75cm. 50 mM sodium phosphate buffer (pH7.8) of hit 1mL was added, and the cell was gathered up using the cel scraper. Ultrasonic crushing was carried out using model GE 50 sonicator (serial 19214C), and it carried out centrifugal [of the suspension of the cell] on 4-degree C conditions for 10000gx 20 minutes. 25mM(s) which furthermore carry out centrifugal [of the supernatant liquid] on 4-degree C conditions for 80000gx 60 minutes, and include precipitation for 0.1% of Triton X-100 It dissolved in sodium phosphate buffer (pH6.8), and considered as the ECE

extract.
(2) Enzyme reaction 0.1 Msodium phosphate buffer (pH6.8), 0.5M The above-mentioned plant extract was mixed so that NaCl, the ECE extract of 2microg, and final concentration might become 1% (v/v), and it pre incubated for 15 minutes at 37 degrees C. Subsequently, after having added 0.1microM Homo sapiens big-end serine 1, being referred to as 100microL and making it react at 37 degrees C for 2 hours, 5mMEDTA was 100microL Added and the reaction was stopped.
(3) The quantum of the endothelin in the reaction mixture obtained by the quantum above of generation endothelin was carried out by the sandwich technique (endothelin 1 measurement kit: IBL) using enzyme immunoassay. That is, 100microL addition of the reaction mixture after the above-mentioned reaction termination and the Homo sapiens endothelin 1 standard solution was done, and they were made to react to 96 hole plate which carried out the solid phase of the rabbit IgG to the Homo sapiens endothelin 1 first at 37 degrees C for 1 hour. The Homo sapiens endothelin 1 standard solution was diluted with 1%BSA and the phosphate buffered saline (pH7.4) which contains Tween 20 0.05%, and was prepared. 0.3microg addition of an anti-endothelin 1 rabbit Fab' peroxidase labelled antibody was done after washing a plate by this phosphate buffered saline (pH7.4), and it was made to react for 30 minutes at 37 degrees C. 100microL addition of O-phenylenediamine (substrate) which dissolved so that it might become 0.4 mg/mL to the hydrogen-peroxide content buffer solution 0.03% after washing a plate by this phosphate buffered saline (pH7.4) was done. After making it react for 15 minutes in a room temperature dark place, 100microL addition of 1-N sulfuric acid was done, and the reaction was stopped. Subsequently, ELISA The absorbance in 490nm was measured using the plate reader (model 3550:Bio-Rad shrine).
(4) The ECE inhibition activity of each plant extract was computed by the following formula by considering the case where the calculation above-mentioned plant extract of ECE inhibition activity is not contained as control. ECE inhibition activity ={1-(absorbance of absorbance/control at the time of containing each plant extract)} x100 (%). A result is shown in Table 1.
[0039]
[Table 1]

植物抽出物	ＥＣＥ阻害活性 (% of control)
セイヨウサンザシ	96.5
ワレモコウ	95.2
チョウジ	91.5
エイジツ	88.9
アセンヤク	81.1
ボダイジュ	47.4
甘草	44.9
ソウハクヒ	40.7
ローズマリー	40.3
アッサムチャ	39.5
シラカバ	39.3
トルメンチラ	37.7
タイム	37.6
ゲンチアナ	37.3
ゲンノショウコ	34.6
ニンジン	33.4
キナノキ	32.8
センブリ	30.7
ツボクサ	28.2
カワラヨモギ	28.1
ジオウ	27.1
スイカズラ	27.0
セイヨウハッカ	25.7

＊各植物抽出物の終濃度が１％となる条件で評価

[0040] Each plant extract showed the outstanding ECE inhibition activity so that more clearly than Table 1. Among these, ECE inhibition activity is 90% or more, and a haw, Sanguisorba officinalis, and caryophylli flos were especially excellent.
[0041]
[Effect of the Invention] If the ECE inhibitor of this invention is used, the conversion to endothelin from a big-end serine can be controlled effectively.

[Translation done.]